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Research Article

Association of T174M polymorphism of angiotensinogen gene with essential hypertension: A meta-analysis

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Abstract

The association between T174M polymorphism of angiotensinogen gene and essential hypertension risk remains controversial. We herein performed a meta-analysis to achieve a reliable estimation of their relationship. All the studies published up to May 2013 on the association between T174M polymorphism and essential hypertension risk were identified by searching the electronic repositories PubMed, MEDLINE and EMBASE, Springer, Elsevier Science Direct, Cochrane Library and Google Scholar. Data were extracted and pooled odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated. Ultimately, nine eligible studies, including 2188 essential hypertension cases and 2459 controls, were enrolled in this meta-analysis. No significant associations were found under the overall ORs for M-allele comparison (M *vs.* T, pooled OR 0.92, 95% CI 0.62-1.37), MM *vs.* TT (pooled OR 0.86, 95% CI 0.29-2.51), TM *vs.* TT n (pooled OR 0.91, 95% CI 0.63-1.32), recessive model (MM *vs.* TT+TM, pooled OR 0.89, 95% CI 0.35-2.30), dominant model (MM+TM *vs.* TT, pooled OR 0.91, 95% CI 0.60-1.38) between T174M polymorphism and risk for essential hypertension. This meta-analysis suggested that the T174M polymorphism of the angiotensinogen gene might not be associated with the susceptibility of essential hypertension in Asian or European populations.

Keywords: essential hypertension, case-control study, T174M, polymorphism, meta-analysis.

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Introduction

Hypertension affects approximately 30% of adults in industrialized countries and is the major risk factor for cardiovascular disease (Nguyen *et al.*, 2013). Hypertension is classified into essential hypertension and secondary hypertension according to the etiology. Secondary hypertension is a type of hypertension caused by an identifiable underlying secondary cause, such as renovascular disease, renal failure, pheochromocytoma, aldosteronism and others, while essential hypertension is defined as hypertension in which secondary causes are not present (Carretero and Oparil, 2000). More than 90% of all hypertensive persons are reported to have essential hypertension (Ghosh *et al.*, 2013). Essential hypertension is associated with large and small vascular remodeling that impacts cardiovascular prognosis (Briet and Schiffrin, 2013). It is generally considered as a paradigmatic multi-factors disease which involves a combination of genetic factors, environmental stimuli and their interaction (O'Shaughnessy, 2001). It has been reported that approximately 20-60% of the inter-individual variation in blood pressure is genetically controlled (Kurtz and Spence, 1993). Thus, we hypothesized that exploring potential hypertension susceptibility genes would help us to better understand the etiology of the disease and, eventually, to better control this disease.

Angiotensinogen (AGT) is a liver protein that interacts with renin to produce angiotensin I, the prohormone of angiotensin II, which is the major effector molecule of the renin-angiotensin-aldosterone system (Gu *et al.*, 2011). It is a promising candidate gene for evaluating susceptibility to essential hypertension (Mohana *et al.*, 2012). T174M polymorphism refers to the substitution of threonine to methionine amino acid at position 174 in exon 2 of the AGT gene. A significant association between T174M polymorphism and the risk of essential hypertension has been reported in several studies (Iso *et al.*, 2000; Jiang *et al.*, 2009). However, several other studies did not detect such an association (Sato *et al.*, 2000; Wang *et al.*, 2002; Nejatizadeh *et al.*, 2008). Therefore, the T174M polymorphism was conflictingly associated with essential hypertension.

In order to achieve an integrative understanding of the association between the T174M polymorphism and the risk of essential hypertension it is necessary to consider the

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findings as a whole, paying special attention to methodological characteristics of each of the studies. Accordingly, we conducted a systematic review of published findings and used meta-analysis techniques to quantitatively combine the results. This allowed us comprehensively investigate the association between T174M polymorphism and the risk of essential hypertension.

Materials and Methods

Sources for the literature search

A literature search was conducted for studies that reported the effect of T174M polymorphism on the risk of essential hypertension. We systematically searched the PubMed, MEDLINE and EMBASE, Springer, Elsevier Science Direct, Cochrane Library and Google Scholar electronic databases for articles published up to May 2013. The following key words were used for searching: "T174M", "hypertension", "angiotensinogen gene", "polymorphism", "variants", "study" or "trial". Furthermore, complimentary searches in the references lists of retrieved papers were performed for any additional studies. The research was restricted to full-text English-language articles of studies in humans.

Search methods

Six investigators (XY. L, ZY. Y, DQ. P, H. D, Y. L and Q. Z) independently searched the electronic databases. The abstracts were first reviewed to obtain potentially eligible articles according to the inclusion criteria. To avoid a possible loss of any relevant article, an additional search was performed through the references cited in identified articles.

Included and excluded criteria of studies

Inclusion criteria of studies

Studies were included in the current meta-analysis if they met the following criteria: (1) the investigated patients suffered from essential hypertension (prospective studies, retrospective studies, or cross-sectional studies, etc.); (2) they evaluated the relationship between T174M polymorphism and essential hypertension risk; (3) they had an odds ratio (OR) with an 95% confidence interval (CI), or other available information for estimating the OR (95% CI); (4) they provided available genotype data for the T174M polymorphism.

Exclusion criteria of studies

Studies were excluded if they met the following criteria: (1) they were designed based on family or sibling pairs; (2) the genotype frequency of the T174M polymorphism was not reported; (3) they did not detect an association between T174M polymorphism and susceptibility of essential hypertension; (4) there was insufficient information for extraction of data.

Evaluation of quality and extraction of data

The quality of the included studies was assessed using a ten-point scoring sheet, as previously described (Clark and Baudouin, 2006). The factors including control group, Hardy-Weinberg equilibrium, case group, primer, reproducibility, blinding, power calculation, statistics, corrected statistics and independent replication were evaluated and the score was recorded as 1 if present or 0 if absent. A final quality score was obtained by summation of each component. Two investigators completed the evaluation independently, and any difference was settled by discussion to reach an agreement between these two investigators.

Two investigators (XY. L and H. Y) independently extracted data according to the inclusion criteria listed above. The extracted data included the first author's name, year of publication, country, sample size, participants, study design, genotyping methods, source of control group, and distribution of T174M polymorphism within the participants of the case *vs.* control group in all studies. Some of these data items were obtained from the author of the primary study. Disagreements were resolved by discussion and reaching an agreement among all investigators, or by contacting the original investigators.

Meta-analysis methods

The strength of the association between T174M polymorphisms and essential hypertension risk was determined by an OR with 95% CI. A chi-square test was used to determine whether or not the observed frequencies of genotypes in the controls conformed to HWE (Hardy-Weinberg expectations), and a p-value < 0.05 was considered as significant disequilib-rium. Pooled ORs were calculated to examine the contrast of A-allele comparison (M *vs.* T), MM *vs.* TT, TM *vs.* TT, recessive model (MM *vs.* TT+TM) and dominant model (MM+TM *vs.* TT), respectively. The significance of pooled ORs was determined by a *Z*-test and a p-value < 0.05 was considered as statistically significant. We assessed the within- and between-study variation or heterogeneity by Cochran's Q-statistic testing (Deeks *et al.*, 2001) and calculating the I^2 index ($I^2 = 100\%(Q\text{-df})/Q$) (Higgins *et al.*, 2003). A significant Q-statistic ($p < 0.10$) or $I^2 > 50\%$ indicated heterogeneity across studies, so the pooled OR estimate was calculated using the random-effects (DerSimonian and Laird, 1986). Otherwise, the fixed-effect (Mantel and Haenszel, 1959) was used. Publication bias was evaluated by using the Egger's linear regression test (Egger *et al.*, 1997), which measures funnel plot asymmetry on the natural logarithm scale of the effect size. Analyses were performed using the STATA software package v.11.0 (Stata Corporation, College Station, TX, USA).

Results

Characteristics of the eligible studies

We retrieved 1037 records that were potentially relevant to the search terms (PubMed: 312; MEDLINE: 136; Springer: 198; Elsevier Science Direct: 105; Cochrane Library: 21; Google Scholar: 265). The study selection process is summarized in Figure 1. After duplicates were removed, this number went down to 129 potentially relevant studies. By screening the abstracts, 89 of these articles were excluded, these including 31 review articles, 23 articles irrelevantto the T174M gene, and 35 articles irrelevantto essential hypertension. The remaining 40 studies were then examined in detail by full text review, this leading to the exclusion of 31 articles, including 17 publications that not about the T174M gene and 14 for not showing available data.

The final result were nine studies (Iso *et al.*, 2000; Sato *et al.*, 2000; Vasku *et al.*, 2002; Wang *et al.*, 2002; Nair *et al.*, 2003; Tsai *et al.*, 2003; Nejatizadeh *et al.*,2008; Jiang *et al.*, 2009; Yuan *et al.*, 2009). These involved 2188 essential hyper cases and 2459 controls, and by meeting the inclusion criteria they were included in this meta-analysis. All of them were case-control studies. The characteristics of these selected studies are summarized in Tables 1 and 2. The included studies were published between 2000 and 2009. The sample sizes ranged from 203 to 919, and source of control groups were normotensives. Eight studies were conducted in Asian populations and one in a European. Furthermore, the observed genotype counts for T174M polymorphisms in each study were all consistent with Hardy-Weinberg disequilibrium ($p > 0.05$).

Meta-analysis of the association between T174M polymorphism and risk for essential hypertension

Crude ORs with 95% CIs were used to assess the association between T174M polymorphism and risk of essential hypertension. Significant heterogeneities were observed across the studies for M-allele comparison (M *vs.* T, $p < 0.01$ and $I^2 = 88.2\%$), MM *vs.* TT comparison ($p < 0.01$ and $I^2 = 73.0\%$), TM *vs.* TT comparison ($p < 0.01$ and $I^2 = 82.9\%$), recessive model (MM *vs.* TT+TM, $p < 0.01$ and $I^2 = 65.4\%$) and dominant model (MM+TM *vs.* TT, $p < 0.01$ and $I^2 = 87.1\%$) (Table 3). Therefore, the random effect model was applied to estimate the overall ORs.

In the present study, no significant difference was observed in the risk of essential hypertension between the genotypes M *vs.* T (pooled OR 0.92, 95% CI 0.62-1.37), MM *vs.* TT (pooled OR 0.86, 95% CI 0.29-2.51), TM *vs.* TT (pooled OR 0.91, 95% CI 0.63-1.32), MM *vs.* TT+TM (pooled OR 0.89, 95% CI 0.35-2.30), or MM+TM *vs.* TT (pooled OR 0.91, 95% CI 0.60-1.38) (Table 3).

We also performed a subgroup analysis stratified by geographic location (ethnicity) and sample size. As shown in Table 3, this refined further analysis still did not indicated an association between T174M polymorphism and essential hypertension risk.

Publication bias

The Egger's test was performed to assess the publication bias of the published studies. For all comparisons, the p value of the Egger's test was higher than 0.05 (Table 4), this indicating that there was no evident publication bias in this meta-analysis.

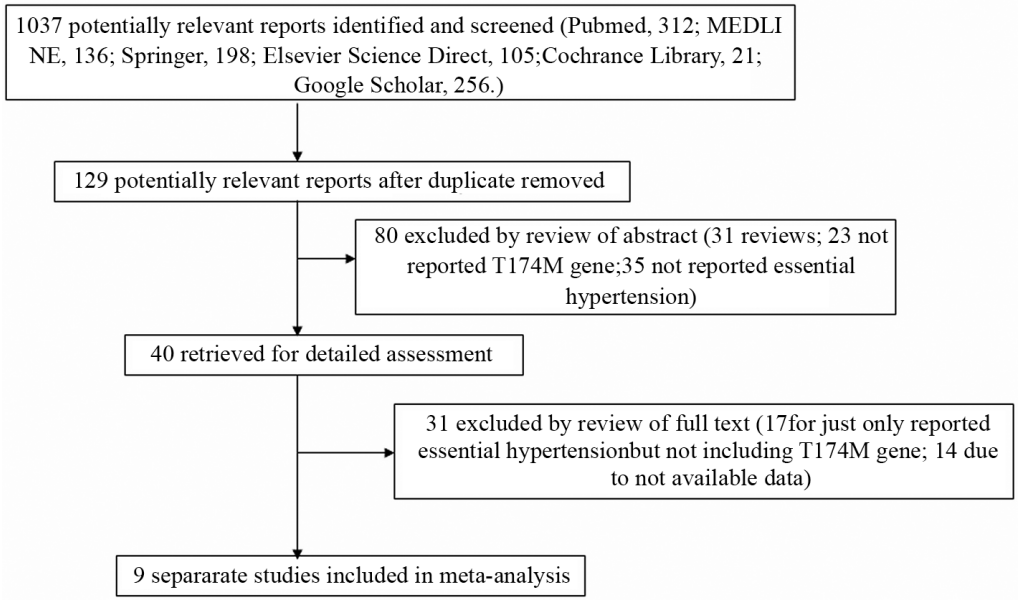

Figure 1 - Flowchart of the selection of studies for inclusion in the meta-analysis.

Table 1 - Characteristics of studies included in the meta-analysis.

Study	Year	Country	Ethnicity	Genotyping methods	Sample size		Source of control	Study design
					Case	Control		
Iso *et al.*, 2000	2000	Japan	Asian	NA	229	690	Normotensives	Case-control
Jiang *et al.*, 2009 [11]	2008	China	Asian	Multiplex PCR	220	235	Normotensives	Case-control
Nair *et al.*, 2003	2003	India	Asian	PCR-based restriction endonuclease digestion method	134	131	Normotensives	Case-control
Nejatizadeh *et al.*, 2008	2008	India	Asian	NA	450	358	Normotensives	Case-control
Sato *et al.*, 2000	2000	Japan	Asian	PCR-RFLP	180	195	Normotensives	Case-control
Tsai *et al.*, 2003	2003	China	Asian	Mini-PCR	408	286	Normotensives	Case-control
Vasku *et al.*, 2002	2002	Czech Republic	European	NA	189	201	Normotensives	Case-control
Wang *et al.*, 2002	2002	China	Asian	PCR amplifications	107	96	Normotensives	Case-control
Yuan *et al.*, 2009	2009	China	Asian	PCR-RFLP	271	267	Normotensives	Case-control

Table 2 - Genotype frequencies of T174M polymorphism in studies included in the meta-analysis.

Study	Year of publication	Case genotype			Control genotype			HWE[a]	
		TT	TM	MM	TT	TM	MM	Chi-square test	p value
Iso *et al.*, 2000	2000	177	50	2	335	289	66	0.10	0.74
Jiang *et al.*, 2009	2009	126	85	9	167	63	5	0.11	0.73
Nair *et al.*, 2003	2003	104	29	1	102	27	2	0.01	0.88
Nejatizadeh *et al.*, 2008	2008	378	67	5	291	61	6	1.73	0.19
Sato *et al.*, 2000	2000	145	31	4	155	38	2	0.04	0.84
Tsai *et al.*, 2003	2003	326	70	12	231	53	2	0.31	0.58
Vasku *et al.*, 2002	2002	142	44	3	147	50	4	0.01	0.92
Wang *et al.*, 2002	2002	91	15	1	79	16	1	0.04	0.85
Yuan *et al.*, 2009	2009	227	44	0	235	32	0	1.08	0.29

[a]HWE: Hardy-Weinberg equilibrium, evaluated using the goodness-of-fit chi-square test. $p < 0.05$ was considered representative of a departure from HWE.

Table 3 - Meta-analysis of the association between T174M polymorphism and risk of essential hypertension using random effect model.

Groups	No. of studies	M *vs.* T				MM *vs.* TT				TM *vs.* TT				MM *vs.* TT+TM				MM+TM *vs.* TT			
		OR(95%CI)	P_A	I^2 (%)	P_H	OR(95%CI)	P_A	I^2 (%)	P_H	OR(95%CI)	P_A	I^2 (%)	P_H	OR(95%CI)	P_A	I^2 (%)	P_H	OR(95%CI)	P_A	I^2 (%)	P_H
Overall	9	0.92 (0.62, 1.37)	0.69	88.2	< 0.01	0.86 (0.29, 2.51)	0.78	73.0	< 0.01	0.91 (0.63, 1.32)	0.62	82.9	< 0.01	0.89 (0.35, 2.30)	0.81	65.4	< 0.01	0.91 (0.60, 1.38)	0.65	87.1	< 0.01
Ethnicity																					
Asian	8	0.93 (0.59, 1.44)	0.73	89.6	< 0.01	0.87 (0.25, 3.04)	0.83	77.0	< 0.01	0.91 (0.60, 1.38)	0.66	85.0	< 0.01	0.91 (0.30, 2.74)	0.86	70.5	< 0.01	0.91 (0.57, 1.46)	0.7	88.7	< 0.01
European	1	0.90 (0.60, 1.36)	0.63	-	-	0.78 (0.17, 3.53)	0.74	-	-	0.91 (0.57, 1.45)	0.70	-	-	0.79 (0.18, 3.60)	0.77	-	-	0.90 (0.57, 1.42)	0.65	-	-
Sample size																					
< 500	5	1.09 (0.82, 1.45)	0.53	47.0	0.11	1.46 (0.70, 3.02)	0.31	0.0	0.64	1.09 (0.79, 1.51)	0.60	47.2	0.11	1.36 (0.66, 2.81)	0.41	0.0	0.74	1.10 (0.79, 1.53)	0.58	51.5	0.08
≥ 500	4	0.79 (0.39, 1.60)	0.52	93.5	< 0.01	0.53 (0.05, 5.76)	0.61	88.9	< 0.01	0.77 (0.41, 1.43)	0.41	89.7	< 0.01	0.61 (0.07, 5.27)	0.65	86.6	< 0.01	0.76 (0.37, 1.56)	0.45	92.7	< 0.01

OR, odds ratio; CI, confidence interval; pH , p value for between-study heterogeneity; PA, p value for test of the association.

Table 4 - Tests for publication bias (Egger's test) in population (overall).

Comparison	Egger's test	
	t	p value
M *vs.* T	0.76	0.47
MM *vs.* TT	-0.20	0.85
TM *vs.* TT	0.84	0.43
MM *vs.* TT+TM	-0.16	0.88
MM+TM *vs.* TT	0.84	0.43

Discussion

The association between the T174M polymorphism and risk for essential hypertension was not clear due to inconsistent data generated by a range of independent studies (Nair *et al.*, 2003; Tsai *et al.*, 2003; Jiang *et al.*, 2009; Nejatizadeh *et al.*, , 2008). Therefore, we performed a meta-analysis of published studies to clarify the inconsistency and to establish a comprehensive picture of this gene-disease association. All studies included in this analysis were conducted in Asian or European populations with high prevalence of essential hypertension. In our meta-analysis, a total of nine studies were included, these comprising 2188 cases and 2459 controls. The conclusion is that no significant association was detected between the T174M polymorphism and essential hypertension risk.

The findings of the present study were different from the results of a previous meta-analysis conducted by Pereira *et al.* (2008), in which a codominant model of T174M polymorphism demonstrated a significant increase in the risk of essential hypertension in Asians (10 studies were included and four of them were Chinese) and in mixed/other populations (including African, Indo-European/East Asian, Russian Arab and Turkish) but not in a population of European descendants. Upon comparing these two meta-analyses, we found that two studies (Morise *et al.*, 1995; Yi-Yang *et al.*, 2006) conducted among Asian populations (one in Japan and one in Chain) were included in the analysis of Pereira *et al.* (2008) but not in ours. These two studies indicated a significantly increased risk of essential hypertension among populations carrying the 174M allele. This may be one reason for the different outcomes of these two meta-analyses. Furthermore, it should be noted that in the study of Pereira *et al.* (2008) a potential publication bias was present.

The AGT gene T174M polymorphism was first reported by Jeunemaitre *et al.* (1992) to be related to the prevalence of essential hypertension. Since then several studies on this relationship, enrolling various ethnic groups, have been published. Some studies confirmed the association between T174M variant and hypertension(Gardemann *et al.*, 1999; Procopciuc *et al.*, 2005), but others did not (Nair *et al.*, 2003; Renner *et al.*, 2005). Moreover, some studies

reached different conclusions, even when they were performed among the same ethnic populations (Qi *et al.*, 2007; Gu *et al.*, 2011). There are several potential explanations for the discrepancies among these studies. The first possible cause may be genetic differences in the population samples and phenotypic differences in the hypertensive populations analyzed (Marco *et al.*, 2005). Second, the effect of the T174M variant on plasma AGT levels may vary among different ethnic groups so that the association between T174M polymorphism and risk of essential hypertension may not be detected in every ethnic group, just as shown in the study of Pereira *et al.* (2008). Most studies included in current meta-analysis were conducted in Asian populations and only one in a European population, this meaning that the final result may not be generalizable. Therefore, more studies need to be performed in various ethnic groups and subgroup analysis stratified by ethnicity should be conducted in future research. Second, the reliability of the findings of a study may be questionable if it lacks an appropriate control group. In some studies, the age and percentage of subjects with alcohol consumption or smoking were significantly different between the hypertensive and control groups (Hingorani *et al.*, 1996; Kiema *et al.*, 1996). A third possible cause of discrepancy may be a multiple interaction of polymorphisms or genes. These gene-to-gene interactions make the association of hypertension with any single candidate gene more complex (Wang *et al.*, 2002). In addition, the numbers of cases were different in various studies, this leading to variation in precision. Finally, hypertension is an acknowledged multifactorial disease. Genetic factors may interact with several other factors, such as salt intake, body mass index, and smoking in the development of hypertension.

Certain limitations of this study need to be mentioned. First of all, heterogeneity across the studies was observed. One possible reason for the presence of heterogeneity is the wide variation in populations included (77.7% in Asian and 11.1% in European). Second, the effect of genetic and environmental interactions was not considered. In addition, all the included articles were case-control studies and the number of studies was small (nine). Therefore, more and high-quality case-control studies are still needed to test and verify the results of this metaanalysis. Finally, our analysis was limited to eight studies on Asian and one on European populations, which is certainly not representative of all ethnicities. The association between the T174M polymorphism and risk of essential hypertension still needs to be clarified.

Despite these limitations, this meta-analysis suggests that the T174M polymorphism of the angiotensinogen gene is not associated with susceptibility of essential hypertension, and the allele M may not increase the risk of essential hypertension in Asian or European populations. Considering the different genetic and phenotypic features among different ethnic groups, larger and well-designed studies based on different populations are needed to confirm our results.

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References

Briet M and Schiffrin EL (2013) Treatment of arterial remodeling in essential hypertension. Curr Hypertension Rep 15:3-9.

Carretero OA and Oparil S (2000) Essential hypertension part I: definition and etiology. Circulation 101:329-335.

Clark MF and Baudouin SV (2006) A systematic review of the quality of genetic association studies in human sepsis. Intensive Care Med 32:1706-1712.

Deeks JJ, Altman DG and Bradburn MJ (2001) Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Altmann DG and Bradburn MJ (eds) Systematic Reviews in Health Care: Meta-Analysis in Context. 2nd edition, BMJ Publ Group, London, pp 285-312.

DerSimonian R and Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177-188.

Egger M, Smith GD, Schneider M and Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315:629-634.

Gardemann A, Stricker J, Humme J, Nguyen QD, Katz N, Philipp M, Tillmanns H, Hehrlein FW and Haberbosch W (1999) Angiotensinogen T174M and M235T gene polymorphisms are associated with the extent of coronary atherosclerosis. Atherosclerosis 145:309-314.

Ghosh R, Bhattacharya M, Khan G, Chakraborty S, Bhattacharya R, Maji UK, Jana P and Sinha AK (2013) Diagnosis of essential hypertension in humans by the determination of plasma renal cortexin using enzyme-linked immunosorbent assay. Clin Lab 59:475-481.

Gu W, Liu Y, Wang Z, Liu K, Lou Y, Niu Q, Wang H, Liu J and Wen S (2011) Association between the angiotensinogen gene T174M polymorphism and hypertension risk in the Chinese population: a meta-analysis. Hypertens Res 35:70-76.

Higgins JP, Thompson SG, Deeks JJ and Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327:557.

Hingorani AD, Sharma P, Jia H, Hopper R and Brown MJ (1996) Blood pressure and the M235T polymorphism of the angiotensinogen gene. Hypertension 28:907-911.

Iso H, Harada S, Shimamoto T, Sato S, Kitamura A, Sankai T, Tanigawa T, Iida M and Komachi Y (2000) Angiotensinogen T174M and M235T variants, sodium intake and hypertension among non-drinking, lean Japanese men and women. J Hypertens 18:1197-1206.

Jeunemaitre X, Soubrier F, Kotelevtsev YV, Lifton RP, Williams CS, Charru A, Hunt SC, Hopkins PN, Williams RR and Lalouel J-M (1992) Molecular basis of human hypertension: role of angiotensinogen. Cell 71:169-180.

Jiang X, Sheng H, Li J, Xun P, Cheng Y, Huang J, Xiao H and Zhan Y (2009) J Association between renin–angiotensin system gene polymorphism and essential hypertension: a community-based study. J Hum Hypertens 23:176-181.

Kiema T-R, Kauma H, Rantala AO, Lilja M, Reunanen A, Kesäniemi YA and Savolainen MJ (1996) Variation at the angiotensin-converting enzyme gene and angiotensinogen gene loci in relation to blood pressure. Hypertension 28:1070-1075.

Kurtz TW and Spence MA (1993) Genetics of essential hypertension. Am J Med 94:77-84.

Mantel N and Haenszel W(1959) Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 22(4):719-748.

Marco J, Zabay J, García-Marco M, Gomez G, Mulet J, Munar M, Soler J and Viader C (2005) Angiotensinogen gene T174M polymorphism: opposite relationships with essential hypertension and obesity in a homogeneous population from Majorca (Balearic Islands, Spain). Nefrología 25:629.

Mohana VU, Swapna N, Surender RS, Vishnupriya S and Padma T (2012) Gender-related association of AGT gene variants (M235T and T174M) with essential hypertension - A case-control study. Clin Exp Hypertens 34:38-44.

Morise T, Takeuchi Y and Takeda R (1995) Rapid detection and prevalence of the variants of the angiotensinogen gene in patients with essential hypertension. J Intern Med 237:175-180.

Nair K, Shalia K, Ashavaid T and Dalal J (2003) Coronary heart disease, hypertension, and angiotensinogen gene variants in indian opulation. J Clin Lab Anal 17:141-146.

Nejatizadeh A, Kumar R, Stobdan T, Goyal AK, Gupta M, Javed S and Pasha MQ (2008) Significance of angiotensinogen gene haplotypes and genotypes combinations in hypertension. J Hypertens 26:1094-1101.

Nguyen K-DH, Pihur V, Ganesh SK, Rakha A, Cooper RS, Hunt SC, Freedman BI, Coresh J, Kao WL and Morrison AC (2013) Effects of rare and common blood pressure gene variants on essential hypertension results from the Family Blood Pressure Program, CLUE, and Atherosclerosis Risk in Communities Studies. Circ Res 112:318-326.

O'Shaughnessy KM (2001) The genetics of essential hypertension. Br J Clin Pharmacol 51:5-11.

Pereira TV, Nunes AC, Rudnicki M, Yamada Y, Pereira AC and Krieger JE (2008) Meta-analysis of the association of 4 angiotensinogen polymorphisms with essential hypertension a role beyond M235T? Hypertension 51:778-783.

Procopciuc L, Pop D, Zdrenghea D and Jebeleanu G (2005) Genetic analysis of angiotensinogen gene polymorphisms (M235T and T174M) in Romanian patients with essential arterial hypertension. Roman J Intern Med 43:61.

Qi Y, Niu W, Zhou W, Hou S and Qiu C (2007) Correlation between angiotensinogen gene polymorphisms and essential hypertension in Chinese population. J Hum Hypertens 22:147-150.

Renner W, Nauck M, Winkelmann BR, Hoffmann MM, Scharnagl H, Mayer V, Boehm BO and März W (2005) Association of angiotensinogen haplotypes with angiotensinogen levels but not with blood pressure or coronary artery disease: the Ludwigshafen Risk and Cardiovascular Health Study. J Mol Med 83:235-239.

Sato N, Katsuya T, Nakagawa T, Ishikawa K, Fu Y, Asai T, Fukuda M, Suzuki F, Nakamura Y and Higaki J (2000) Nine polymorphisms of angiotensinogen gene in the susceptibility to essential hypertension. Life Sci 68:259-272.

Tsai C-T, Fallin D, Chiang F-T, Hwang J-J, Lai L-P, Hsu K-L, Tseng C-D, Liau C-S and Tseng Y-Z (2003) Angiotensinogen gene haplotype and hypertension interaction with ACE gene I allele. Hypertension 41:9-15.

Vasku A SM, Tschöplová S and Stejskalová A (2002) An association of BMI with A (-6) G, M235T and T174M polymorphisms in angiotensinogen gene in essential hypertension. J Hum Hypertens16:427-430.

Wang J-H, Lin C-M, Wang L-S, Lai N-S, Chen D-Y and Cherng J-M (2002) Association between molecular variants of the angiotensinogen gene and hypertension in Amis tribes of eastern Taiwan. J Formosan Med Assoc101:183-188.

Yi-Yang Z XJ, Hai-hui S, Gang L, Yun-lin C and Jun H (2006) Association between partial indexes of angiotensinogen gene polymorphisms and the risk of essential hypertension: a community case-control study. Chin J Clin Rehabil 10:5.

Yuan J, Tang W, Chun Y, Ying H, Yang Y and Xiao C (2009) Angiotensinogen T174M and M235T variants and hypertension in the Hani and Yi minority groups of China. Biochem Genet 47:344-350.

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